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10/040,803	01/07/2002	Andrew Darrow	ORT-1562	4825
7590	04/05/2004		EXAMINER	
Philip S. Johnson, Esq. Johnson & Johnson One Johnson & Johnson Plaza New Brunswick, NJ 08933-7003			MOORE, WILLIAM W	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/040,803

Applicant(s)

DARROW ET AL.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15, 16 and 28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15, 16 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>07/21/2003</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Amendment

Applicant's Amendments to the Title of the application and to claims 15 and 16, and introducing the new claim 28, filed December 11, 2003, have been entered, overcoming the rejections of record under 35 U.S.C. § 112, first and second paragraphs. Claims 15, 16 and 28 are now pending herein. The amendment to claim 15 and the new claim 28 necessitate restatement of prior art rejections of record which are maintained based on principles of inherency where only the eight amino-terminal amino acids differ between the mature serine proteases released by post-translational processing of the amino acid sequences set forth in SEQ IDs NO:7 and 8 herein and these octapeptide amino-termini are too distant from the catalytic site to influence C-E proteolytic specificity. Absent a showing to the contrary, assays conducted with serine proteases comprising the nearly identical amino acid sequences released by post-translational processing of both the native protease of SEQ ID NO:7 and the fusion polypeptide having the amino acid sequence of SEQ ID NO:8 herein are inherently the same assay. Consequently, they are inherently the same as, and indistinguishable from, assays of the rejected claims conducted with a serine protease comprising a catalytic domain released by post-translational processing of the prior art proteases of Botstein et al., Chen et al. and Antalis et al., because each is identical to a catalytic domain released by post-translational processing of the native C-E protease of SEQ ID NO:7. Because a new ground of rejection is set forth herein, this communication is not made final.

Claim Objections

Claim 28 is objected to because of the following informalities: The word nitroaniline is misspelled. Appropriate correction is required.

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 16, and 28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is not enabling for a method of identifying compounds that activate, or enhance the activity of, a serine protease C-E and does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

Claims 15, 16, and 28 embrace methods of identifying both candidate activators and candidate inhibitors. It is agreed that compounds that can inhibit serine protease activity are well-known in the art, as are methods for identifying compounds that inhibit the activity of a particular serine protease. Yet neither the specification nor the prior art of record herein suggest that the art is aware of any class of compounds capable of activating or augmenting serine protease activity, or that an artisan could know what might be a test compound that can be used in an assay to detect an activator of the serine protease activity of protease C-E. It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. § 112, first paragraph, for non-enablement. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "Forman" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). Applying the "Forman" factors discussed in *Wands*, *supra*, to Applicant's disclosure, it is apparent that:

- a) the specification lacks adequate, specific, guidance for selecting even a potential compound that might be identified as an activator of serine protease activity in a claimed method,

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- b) the specification lacks working examples wherein any class of compounds from which potential serine protease activator might be drawn is discussed, or where any activator of serine protease activity is assayed in a claimed method,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such selection, and,
- d) unpredictability exists in the art where no activators of serine protease activity have been identified.

Thus the specification cannot support the scope of subject matter embraced by the phrase, "modulate serine protease C-E activity", even if combined with the prior art. Amending claim 15 to describe a method of identifying compounds that inhibit serine protease C-E activity will overcome this rejection.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 16 and 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite because it is incomplete where it does not require a comparison of the rate of change in a property of a labeled substrate between a control assay where a candidate modulator is absent and the labeled substrate present and an assay where both the candidate modulator and the labeled substrate are present. Such a process may be included either in the claim preamble or in step (b) of claim 16, or introduced as a separate step, in order to overcome this aspect of the rejection. Claim 16 is indefinite in two ways. First, the claim recites an improper Markush group where a general class of assay, a fluorogenic assay, is recited together with a subclass within this class, a fluorescent resonance energy transfer assay (FRET). Removing the subclass from claim 16 and presenting it in a dependent claim will address this aspect of the rejection. Second, the claim is improperly dependent from claim 15 because only two classes of assays recited permit a measure of a change in a labeled substrate when it is maintained in a combination together with the protease and a candidate modulator is present or absent while the third, a radiometric assay, requires a further, separation,

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step for measuring the released radiolabel of the substrate. Presenting a separate independent claim describing a radiometric assay, e.g., in parallel with a claim 15 amended as suggested hereinabove, and adding a separation step for the radiolabel will overcome this aspect of the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 15, 16, and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Botstein et al., WO 99/35170, of record, in view of Nelson et al., US 5,242,463, made of record herewith.

Applicant's arguments with respect to the prior art rejection of record of claims 15 and 16 over Botstein et al. have been considered but are moot in view of the new grounds of rejection necessitated by the amendment to claim 15, and the introduction of claim 28, filed December 11, 2003. The teachings of Botstein et al. discussed in the rejection of record set forth in the communication mailed July 7, 2003, are taken as before, in particular their teaching of the nucleotide sequence of a cDNA encoding a medically important, human serine protease PRO343 which has an amino acid sequence identical to that of the C-E protease herein. See, Figures 11, 12 & 34, SEQ IDs NOs:11 & 12, and at pages 18-20, 22-27, 31-44 and 48. As explained above, proteolytic activities of the catalytic domain of the native PRO343/C-E protease catalytic domain released by

post-translational processing and the catalytic domain of the fusion polypeptide of SEQ ID NO:8 released by post-translational processing are indistinguishable in assays of claims 15, 16 and 28 herein absent a showing to the contrary. Botstein et al. also teach, at pages 31-33, that the PRO343 protease should be used in assays to identify compounds that may "interfere with", i.e., modulate, its protease activity. Nelson et al. teach, col. 6, lines 7-42, Examples 2 and 3 at cols. 8-11, and claim 1, that the protease activity of a mammalian serine protease may be assayed fluorogenically to detect compounds that modulate its activity by monitoring changes in the fluorescence of a para-nitroaniline-labeled peptide substrate incubated with the serine protease and candidate modulatory compounds.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Nelson et al. in fluorogenic assays to detect modulators of the activity of the PRO343 protease of Botstein et al. by incubating the protease, a candidate modulator compound, and a para-nitroaniline-labeled peptide substrate and monitoring changes in the fluorescence generated by cleavage of the substrate, an assay that is inherently the same assay conducted with the catalytic domain amino acid sequence set forth in SEQ ID NO:8 herein of claims 15, 16 and 28. This is because Botstein et al. teach that the PRO343 protease should be used in an assay to identify compounds that modulate its protease activity and because such an artisan would have been motivated to use the methods of Nelson et al. to do so, appreciating that the methods of Nelson et al. would be appropriate and efficacious in identifying compounds that modulate protease activity of mammalian serine proteases, such as the PRO343 protease of Botstein et al.

Claims 15, 16, and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen et al., WO 99/14328, of record in view of Nelson et al., US 5,242,463, cited above.

Applicant's arguments with respect to the prior art rejection of record of claims 15 and 16 over Chen et al. have been considered but are moot in view of the new grounds of rejection necessitated by the amendment to claim 15, and the introduction of claim 28, filed December 11, 2003. Teachings of Chen et al., discussed in the rejection of record set forth in the communication mailed July 7, 2003, are taken as before, in particular their teaching of the nucleotide sequence of a cDNA encoding a medically important human serine protease PRO343 having an amino acid sequence identical to that of the C-E protease herein. See Figures 97 & 98, SEQ IDs NOs:262 & 263, and pages 29, 49-50, 59, 61-68, 79, 92-99. As explained above, proteolytic activities of the catalytic domain of the native PRO343/C-E protease catalytic domain released by post-translational processing and the catalytic domain of the fusion polypeptide of SEQ ID NO:8 released by post-translational processing are indistinguishable in assays of claims 15, 16 and 28 herein absent a showing to the contrary. Chen et al. further teach, at pages 31-33, that the PRO343 protease should be used in an assay to identify compounds that may "interfere with", i.e., modulate, the protease activity of the PRO343 protease. Nelson et al. teach, col. 6, lines 7-42, Examples 2 and 3 at cols. 8-11, and claim 1, that the protease activity of a mammalian serine protease may be assayed fluorogenically to detect compounds that modulate its activity by monitoring changes in the fluorescence of a para-nitroaniline-labeled peptide substrate incubated with the serine protease and candidate modulatory compounds.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Nelson et al. in fluorogenic assays to detect modulators of the activity of the PRO343 protease of Chen et al. by incubating the protease, a candidate modulator compound, and a para-nitroaniline-labeled peptide substrate and monitoring changes in the fluorescence generated by cleavage of the substrate, an assay that is

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inherently the same assay conducted with the catalytic domain amino acid sequence set forth in SEQ ID NO:8 herein of claims 15, 16 and 28. This is because Chen et al. teach that the PRO343 protease should be used in an assay to identify compounds that modulate its protease activity and because such an artisan would have been motivated to use the methods of Nelson et al. to do so, appreciating that the methods of Nelson et al. would be appropriate and efficacious in identifying compounds that modulate protease activity of mammalian serine proteases, such as the PRO343 protease of Chen et al.

Claim 15, 16, and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Antalis et al., WO 98/36054, of record, in view of Nelson et al., US 5,242,463, cited above.

Applicant's arguments with respect to the prior art rejection of record of claims 15 and 16 over Antalis et al. have been considered but are moot in view of the new grounds of rejection necessitated by the amendment to claim 15, and the introduction of claim 28, filed December 11, 2003. Teachings of Antalis et al. discussed in the rejection of record set forth in the communication mailed July 7, 2003, are taken as before, in particular their teaching of the nucleotide sequence of a cDNA encoding a medically important human serine protease SPO01LA having a deduced amino acid sequence that is identical to the amino acid sequence of the native C-E protease from position 47 to position 317, see Figure 20A, SEQ ID NO:28, pages 18 and 52-53 and claims 19-21, 26, and 27, thus catalytic domains of the SPO01LA protease and the protease C-E disclosed herein are identical. As explained above, proteolytic activities of the catalytic domain of the native SPO01LA/C-E protease catalytic domain released by post-translational processing and the catalytic domain of the fusion polypeptide of SEQ ID NO:8 released by post-translational processing are indistinguishable in assays of claims 15, 16 and 28 herein absent a showing to the contrary. Antalis et al. further teach, pages 25-26, the need to find agonists, antagonists, and other modulatory compounds that can alter the activity of a

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disclosed SPO01LA protease. Nelson et al. teach, col. 6, lines 7-42, Examples 2 and 3 at cols. 8-11, and claim 1, that the protease activity of a mammalian serine protease may be assayed fluorogenically to detect compounds that modulate its activity by monitoring changes in the fluorescence of a para-nitroaniline-labeled peptide substrate incubated with the serine protease and candidate modulatory compounds.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Nelson et al. in fluorogenic assays to detect modulators of the activity of the SPO01LA protease of Antalis et al. by incubating the protease, a candidate modulator compound, and a para-nitroaniline-labeled peptide substrate and monitoring changes in the fluorescence generated by cleavage of the substrate, an assay that is inherently the same assay conducted with the catalytic domain amino acid sequence set forth in SEQ ID NO:8 herein of claims 15, 16 and 28. This is because Antalis et al. teach that it is necessary to find compounds that modulate the activity of the SPO01LA protease and because such an artisan would have been motivated to use the methods of Nelson et al. to do so, appreciating that the methods of Nelson et al. would be appropriate and efficacious in identifying compounds that modulate protease activity of mammalian serine proteases, such as the SPO01LA protease of Antalis et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
March 31, 2004


NASHAAT T. NASHED PHD.
PRIMARY EXAMINER